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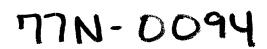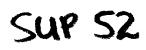Rockville, Maryland 20852
USA

21st April 2004

Dear Sir or Madam

Thrombosis Prevention Trial

In sending you the accompanying documents about the Thrombosis Prevention Trial for consideration by the Committee, will you please note the following points.

1. Following closure of the Medical Research Council Epidemiology and Medical Care Unit (referred to in the study synopsis paper), other staff involved were re-deployed or took early retirement. All the records have been archived in one of the Unit's previous locations (Northwick Park Hospital, Harrow) and can be accessed only with some difficulty. I am confident that all the main details I have given in the synopsis are accurate but there may be one or two less important points (such as the exact date of the entry of the last man into the trial) which are approximate and would need a good deal of further work to check on, if it were important that they were entirely accurate.

2. Particularly at the time funding for the trial was being requested from the Medical Research Council and the British Heart Foundation, the necessary documentation was much less than it is now and considerably less than the documentation characteristic of applications in the United States. Consequently, the enclosed proposal also acted as the protocol for the trial. (The pilot trial report referred to describes the warfarin only component but includes eligibility, exclusion criteria, establishing risk and other general design aspects applicable to aspirin as well.) There were very few departures from this proposal/protocol influencing the design or conduct of the study. Total man-years in the trial (including, as planned, warfarin component) were 36,000 rather than 40,000. In about 1994, we actively advised all the participating general practitioners to prescribe aspirin for patients with angina pectoris, which had previously been more freely at their discretion. This is one reason for the higher than anticipated proportions withdrawing from randomised treatment (although all continued to be followed up for fatal events and all but about 1% for non-fatal events). However, as indicated in the synopsis, most withdrawals took place after men had been in the trial for some time, so that about two-thirds of the total man-years available were spent on randomly allocated treatment. The nurses in the coordinating centre in the MRC Unit did send out fairly frequent memoranda to the research nurses in the separate general practices with information or

revised instructions about practical management questions, e.g. using the transport system for sending blood samples. These are probably available in the archive if necessary. There was also a very detailed operating manual for individual research nurses in the practices and this too could probably be provided although it is bulky and would involve a considerable photocopying job.

3.   I cannot emphasise too strongly that it would be quite inappropriate for silent myocardial infarction (MI) to be included in analyses of the main outcomes, which were clearly defined as major clinical events, i.e. coronary death and myocardial infarction. I cannot stop the Committee's statistician including silent MIs with the major clinical events, as he did in the documents and in his presentation for the meeting in December 2003, but the Committee several times emphasised the importance of sticking to pre-specified definitions of outcome. We did not specify silent MI as such and it would be a continuing misuse of our data to do so again. I have explained why we included – very briefly – our results on silent MI in the synopsis. (All the possible main outcome events were reviewed by an independent assessor who did not know the treatment group allocations. Fatal events include those where there was autopsy evidence of recent coronary artery thrombosis and/or myocardial infarction. Fatal events also included episodes of myocardial infarction without autopsy that were fatal within a month, although nearly all of these occurred within 24 hours. It has always been our view that there is no clear distinction between sudden coronary death and fatal myocardial infarction in terms of risk factors or pathology and we have always adhered to this convention. Non-fatal MI was defined (see paper) as two out of three of typical chest pain, enzyme changes and electrocardiographic (ECG) changes.)

4.   It is a mistake to assume that if the proportionate reductions in outcome that are used in the planning stage of a trial are not achieved, the trial has failed in its objectives. This assumption is what was considered beforehand might be observed, but once it has been made and used to begin with, it ceases to have any relevance. It is justifiable to establish and assess the significance of the observed results, whether these are greater or less than originally assumed. In any case the reduction in non-fatal events attributable to aspirin, which we always intended to look at separately, was, at 32%, much the same as the 30% used in the sample size estimate.

Yours faithfully

Professor Tom Meade

c.c.   Dr. Steve Weisman

ASPIRIN PRIMARY PREVENTION OF CHD
STUDY SYNOPSIS

Re: Docket 77N-0094

Title of Study: Thrombosis Prevention Trial (TPT)

Principal/Investigator(s): Professor T. W. Meade

Coordinating Center:
MRC Epidemiology and Medical Care Unit. The Unit was formerly based in the Wolfson Institute of Preventive Medicine, Charterhouse Square, London EC1M 6BQ. Following the Director's retirement in 2001 (in accordance with the Medical Research Council's general policy on retirement of Directors), the Unit was closed. Present location details for Professor Meade, who is now Emeritus Professor of Epidemiology, are: Non-communicable Disease Epidemiology Unit, Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK; tel +44 (0)20 7927 2182; fax +44 (0)20 7580 6897, email tom.meade@lshtm.ac.uk .

Publication (reference):
Thrombosis Prevention Trial: Randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. A report from the MRC's General Practice Research Framework. Lancet, 1998;351:233-241. (copy attached)

Studied period (years):
Median 6.8 years
Date of first enrollment:
1984 for trial of anticoagulation only. 1989 for factorial trial including both oral anticoagulation and aspirin. Please see paper for details. Entry to the trial was completed mainly in 1992, with a very small number of men entered in 1993.
Date of last completed (i.e. follow-up):
1997

Objectives:
To demonstrate a 30% reduction in major events of ischaemic heart disease, whether of all events both fatal and non-fatal, or of fatal and non-fatal episodes separately. Please see covering letter.

Methodology:
Randomised, placebo-controlled trial with four treatment groups: (1) active warfarin and active aspirin (WA); (2) active warfarin, placebo aspirin (W); (3) placebo warfarin, active aspirin (A); and (4) placebo warfarin, placebo aspirin (P).

Number of patients:
Planned: Between 5,500 and 6,000 men
Analyzed: 5,499 men altogether, 5,085 for aspirin

Study population:
_100_% male ___% female
Mean age:
57.5 years
Cardiovascular risk at baseline:
About 1.2% per annum (all events, fatal and non-fatal combined). Men selected from the 20% at highest risk based on entry measurements of smoking history, family history, body mass index, systolic blood pressure, serum cholesterol, plasma factor VII activity, plasma fibrinogen level.

Test products, dose, and mode of administration:
1. (Oral) aspirin 75mg daily in controlled release formulation; 2. (Oral) warfarin to an International Normalised Ratio (INR) of about 1.5. Doses to achieve INR of 1.5 ranged from 0.5mg to 12.5mg daily.

Duration of treatment:

Ideally, for the whole of the time men were in the trial. Because of withdrawals from randomised treatment (inevitable in a long term primary prevention trial) the duration for many men was less. However, about two-thirds of the total of the man-years in the trial were spent on randomly allocated treatment.

Criteria for evaluation:

Efficacy: See above. 30% reduction in all events, whether fatal or not, or in fatal events alone or in non-fatal events alone.
Safety: Proportions of men in each group experiencing either major, intermediate or minor bleeding episodes (for definitions, see paper on main results, attached).

Statistical methods:

(1) Analysis according to factorial design, i.e. WA + W cf. A + P for main effect of warfarin; or (2) WA + A cf. W + P for main effect of aspirin. (3) Comparison of four separate treatment groups, i.e. WA, W, A and P where appropriate (bleeding).
Differences in rates compared by log-rank tests.

STUDY SYNOPSIS

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Main effect of aspirin on IHD (WA and A cf. W and P) was a reduction in all IHD (fatal or non-fatal) of 20% (95% CI 1 to 35, p=0.04), 32% reduction in non-fatal events (95% CI 12 to 48, p=0.004). Non-significant increase in fatal events of 12% (95% CI -63 to 22). Absolute reduction in all IHD events of 2.3 per 1,000 man-years (95% CI 0.1 to 4.5), of 2.7 for non-fatal events (95% CI 0.9 to 4.5) and increase of 0.4 (95% CI -1.7 to 0.9) in fatal events. Although it is given in the paper, it is wrong (as happened at the December 2003 meeting) to place much if any emphasis on the separate group result for aspirin and IHD, i.e. A cf. P, of a non-significant reduction of 23% (95% CI -3 to 42). The effect must principally be judged by the main analysis based on all four groups and the larger number of events. (However, the 23% figure obviously differs insignificantly from 20%.)
For stroke, 3% reduction in all events (95% CI -45 to 35), absolute reduction per 1,000 man-years 0.1 (95% CI -1.1 to 1.3). Haemorrhagic stroke – these were strongly influenced by concurrent warfarin treatment. So although there were nine and one events respectively in the active (WA + A) and placebo aspirin (W + P) groups according to analysis of main results, seven of the nine events occurred in those also taking warfarin (WA) compared with no events in those on double placebo treatments (P). Other cardiovascular events (e.g. ruptured aortic aneurysm) were 10 and 12 in active (WA + A) and placebo (P) aspirin groups respectively, with four in aspirin only group (A + P) compared with five in double placebo group (P).

SILENT MI INCLUSION OR EXCLUSION RATIONALE:

It was never intended that these would definitely be included and it was certainly not planned (see absence of any mention in proposal/ protocol) that they would be included along with fatal or non-fatal episodes in the main results. Men had routine electrocardiograms (ECGs) at entry and at their annual medical checks. Colleagues suggested that because of interest in silent MI, a brief note about the results should be included in the paper and there were no differences between the four treatment groups. All men who had a silent MI at some stage during the trial were included. However, the ECG evidence of silent MI (always assessed according to Minnesota code by independent reader) was variable, i.e. a man might show such evidence one year but not the next. It would be a serious misuse of our data for silent events to be included along with the main events, as happened in the FDA Cardiovascular and Renal Drugs Advisory Committee meeting in December 2003. Please consult Professor Meade again if there is any further intention to include these events. While silent MI appears to be a risk factor for a major event later, it does not necessarily follow that it will respond to aspirin in the same way as major events.

SAFETY RESULTS:

(Analysed only in four separate treatment groups because of some interactions between active warfarin and active aspirin) Five major upper gastrointestinal events in aspirin only group (A + P) compared with one in double placebo group (P) with single fatal event in P. For all major extra-cranial events, i.e. gastrointestinal, renal-tract cancer and other events, there were eight in the A + P group and four in the P group. For intermediate events, there were 48 in the A + P group compared with 33 in the P group, the difference being mainly accounted for by less serious gastrointestinal episodes (often haemorrhoids) and genitourinary events, i.e. haematuria. For minor events, 484 men reported these in the A + P group compared with 398 in the P group, the excess being mainly due to nose bleeds, rectal bleeding (mainly haemorrhoids) and easy bruising.

CONCLUSIONS:

75mg aspirin daily significantly reduces all events (fatal and non-fatal combined) by about 20%. However, this reduction is entirely due to the reduction of 32% in non-fatal events. In 1,000 men taking it for a year, aspirin would lead to the avoidance of about three major clinical episodes of IHD, all non-fatal. Only a small reduction is inevitable in primary prevention, where the natural incidence of events is low. This benefit has to be considered together with the risk of serious bleeding and results from other trials as well as TPT suggests that there is a positive benefit in those at demonstrably increased risk, although so far free of clinical episodes.

There was a positive reason for considering fatal and non-fatal events separately, as well as together. This was that the secondary prevention trials, of which there have been many and which have been considered in overviews, show a smaller reduction in fatal than non-fatal episodes and it was clearly important to see whether this difference would also be seen in primary prevention. The protocol makes it clear that analysis of fatal and non-fatal episodes would be carried out separately (p9) and this is also stated in the paper with the main results.

There was deliberately no analysis of all cardiovascular disease (CVD) events. This decision was because of the possible contrast between results of fatal and non-fatal episodes, already referred to, the possibility that haemorrhagic strokes might be increased and some uncertainty about the effects of aspirin on all strokes. So it seems inappropriate to consider all CVD events, unless the analysis is qualified to indicate they may result from benefits, hazards and neutral effects. The point was raised during the brief discussion of the Thrombosis Prevention Trial at the meeting in December 2003 and there was inadequate time then to explain why there was no analysis of all cardiovascular events. During the discussion, undue emphasis was placed by one of the Committee members on the main analysis showing an apparent excess of cardiovascular events due to aspirin. This comment did not take account of the (non-significant) increase in fatal events in the active aspirin group, very possibly a chance occurrence, or, in particular, of the excess of haemorrhagic strokes due to the inclusion in the main analysis of events in those taking combined warfarin and aspirin (W+A treatment).

Protocol and Protocol Amendments: Attached

_____   _____
Signature   Date

Study Contact for FDA follow-up:
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PROPOSAL FOR FACTORIAL RANDOMIZED CONTROLLED TRIAL OF LOW DOSE

WARFARIN AND LOW DOSE ASPIRIN IN THE PRIMARY PREVENTION OF

ISCHAEMIC HEART DISEASE IN MEN AT HIGH RISK

T W Meade

SCIENTIFIC CASE

INTRODUCTION

About half of those experiencing a first heart attack die during that episode and, of these, about half die suddenly. It is this pattern that has prompted so much attention to the primary prevention of ischaemic heart disease (IHD). Prevention through life-style modification would be ideal and is likely to account for at least part of the decline in IHD mortality in several countries. Even where these improvements have occurred, however, IHD is still endemic and in many countries incidence is rising. Trials of clofibrate, cholestyramine and aspirin in primary prevention attest to the eed, in some circumstances, to consider pharmacological intervention.

This proposal is for a factorially designed randomized controlled trial of low dose warfarin and low dose aspirin in the primary prevention of IHD in men at high risk.

Historically, the starting-point for the proposal has been the pilot trial of low dose warfarin in primary prevention. Because of the controversial nature of the value of oral anticoagulants in IHD, the MRC Epidemiology and Medical Care Unit (EMCU) submitted its proposal for a pilot trial to the Systems Board (although additional finance from the MRC was not required). The Board agreed that the pilot trial could be undertaken. This work has now been satisfactorily completed and is described in the accompanying report, which will shortly be published in the European Heart Journal. As it became clear that a full-scale low dose warfarin trial was feasible, consideration was given to using the opportunity for the evaluation of other agents as well and this led to the proposed inclusion of low dose aspirin in a factorial design.

WARFARIN

There are two main reasons for considering the evaluation of warfarin in primary prevention.

1. Results of previous trials. In the secondary prevention trials after myocardial infarction, there was a reduction in mortality of about 20% attributable to oral anticoagulants, this figure depending on the pooling of results from several different trials (1,2). What is much less generally appreciated is that the incidence of recurrent myocardial

infarction and also of other thrombo-embolic episodes including stroke and deep vein thrombosis was reduced by an average of about 50%, this benefit being statistically significant in many of the individual trials in question (e.g. 3,4). There is no evidence that this contrast — the 50% benefit in the case of thrombo-embolic episodes compared with 20% for mortality — is due to biased assessments of outcome or to other technical considerations. The most likely explanation is that many deaths soon after myocardial infarction are electrical in nature and therefore not preventable by anti-thrombotic agents. (The same kind of contrast is seen in the case of aspirin.) Recurrent myocardial infarction, about 80% of strokes and all deep vein thromboses (by definition) are, on the other hand, thrombotic in origin. Since it is with the initial thrombotic contribution to heart attacks that the proposed trial would be concerned, the indications of the secondary prevention trials suggest that oral anticoagulants might be very effective in primary prevention, bearing in mind that there is a thrombotic component in nearly all coronary deaths (5) as well as in myocardial infarction. The striking effects of oral anticoagulants against thrombo-embolic events in the secondary prevention trials were achieved despite the likelihood that anticoagulation may sometimes have been inadequate, at any rate according to the levels that were intended. As Mitchell has pointed out (6), this is particularly likely to have been true of the MRC's short-term trial in which there was, nevertheless, a significant reduction of about 50% in thrombo-embolic episodes attributable to anticoagulants (7). It is, therefore, also from the secondary prevention trials that the first hint arises of the possible effectiveness of lower than conventional levels of anticoagulation.

2. __Factor VII coagulant activity, VII_c, hypercoagulability and IHD.__ Factor VII is the vitamin K dependent pro-coagulatory clotting factor the activity of which is most rapidly and extensively lowered by warfarin.

In 1980 (8) and then, with its principal results, in 1986 (9) EMCU's Northwick Park Heart Study (NPHS) showed a strong and independent relationship between VII_c and the risk of IHD (myocardial infarction or sudden coronary death) within the next five years. This observation raises the possibility that the risk of IHD might be lowered by a reduction of VII_c but not as far as the levels found in conventional, full dose anticoagulation. Since the first report from NPHS (8), and in

many cases in direct response to its results, several other groups have now also reported findings that are consistent in suggesting an association between high VII_c levels and risk of IHD and that this association is likely to be of causal significance (10-32).

Lower dose warfarin. It is probable that different intensities of anticoagulation are appropriate in different circumstances. Thus, anticoagulation to prevent thrombosis associated with artificial valves almost certainly needs to be more intense than for the prevention of recurrent venous thrombosis. It is therefore not unreasonable to consider the possibility that anticoagulation for the prevention of an initial thrombus may need to be less intense. Evidence favouring the use of lower doses includes:

(a) NPHS results. These have already been referred to. The mean VII_c level in those who subsequently experienced a first episode of IHD was 117%. Full dose anticoagulation results in levels of about 30%. In ethnic group comparisons within or related to NPHS, the mean VII_c level in blacks (in the UK and in Gambia) at low or negligible risk of IHD is about 70% of standard (33,34,35) and it is this level that the low dose warfarin trial aims to achieve.

(b) Venous thrombosis prophylaxis. In two randomized controlled trials of the prophylaxis of venous thrombosis (36,37), levels of anticoagulation less intense than those conventionally used were deliberately induced. They were found to be equally effective in preventing thrombosis but were also associated with a reduction in bleeding episodes. Of particular interest is a very recent trial of "fixed mini dose" warfarin in which a daily dose of 1 mg warfarin was compared with (a) full dose anticoagulation and (b) no treatment in a randomized controlled trial of the prevention of deep vein thrombosis in patients undergoing major gynaecological surgery (38). There was a significantly lower incidence of deep vein thrombosis in the mini dose warfarin and full dose anticoagulant treatment groups than in the controls, the proportions developing ^{125}I-fibrinogen positive scans being 9%, 3% and 30% respectively. Mean haemoglobin concentrations fell in all three groups but significantly less in the mini dose group than after full anticoagulation. The results of this trial suggest that even lower doses than those we are proposing may be effective but, whether or not this may eventually be shown to be so, the results of the Manchester trial (38) provide strong additional evidence in favour of our approach.

(c) **Embolism.** Very recently, another trial (39) has shown that antico-agulation less intense that conventionally used is equally effective in preventing embolism after tissue valve replacement and that it causes significantly less bleeding.

(d) **Secondary prevention trials.** Attention has already been drawn to the indications from at least one of these trials that the striking benefits of oral anticoagulants against thromboembolic episodes may have been achieved despite levels of anticoagulation considerably less than originally intended.

Hazards of oral anticoagulants. The main hazard of oral anticoagulants is bleeding. While it is clearly not possible to guarantee that anticoagulation of the intensity proposed in this trial would never lead to serious bleeding, the results summarised in the report of the pilot trial are generally reassuring. The results of a special study carried out for us by Dr Christopher Hawkey in Nottingham are also entirely reassuring so far as the effect of warfarin on gastric bleeding is concerned (see below).

A rare complication of full oral anticoagulation is skin necrosis. This is probably due to a deficiency of protein C coupled with the relatively abrupt onset of anticoagulation that is produced by high loading doses, since recurrence can be prevented by gradual induction of anticoagulation (40). We do not screen participants for protein C (although we could do so at some additional cost), but our induction of anticoagulation is very gradual (see report of pilot trial). The risk of skin necrosis is therefore likely to be very remote. It has also been suggested that because of their effect on protein C, oral anticoagulants may promote rather than prevent thrombosis until the INR is more than about 2.0. The trials summarized in (b) - (d) (above) strongly suggest, however, that the net effect of low doses is beneficial.

Warfarin may very occasionally cause hair loss. This effect is dose related and reversible.

ASPIRIN

As it became increasingly clear that a low dose warfarin trial is feasible, the possibility of also evaluating other agents was raised, bearing in mind the many pathways in the pathogenesis of IHD. One approach is to consider

modifying the other main component of the haemostatic system, i.e. platelet function, by low dose aspirin, thus aiming for a definitive trial of the primary prevention of IHD by low dose anti-thrombotic measures. On full consideration, this is the course we have adopted. This decision is now supported by the results and conclusions of recently published trials of aspirin (41,42,43,44). In secondary prevention (i.e. after myocardial infarction, transient ischaemic attacks or unstable angina), aspirin reduces rates of recurrence or progression by about 25%. However, the review on which this conclusion is based (41) emphasises that while there is no doubt as to the value of aspirin in patients who already have evidence of occlusive vascular disease, the balance of risk and benefit might be different in primary prevention where the absolute risk of events is lower and where any benefit may not neccessarily outweigh the risk of bleeding. One of the characteristics of the two primary prevention trials now reported, in British and American doctors (43,44), was the very low event rate, particularly in the American trial. While this trial certainly indicated a reduction in incidence attributable to aspirin (a finding with which the results of the British trial are compatible, though not significant on their own), both trials suggested the possibility of an increase in the incidence of disabling or haemorrhagic stroke that might be due to aspirin. The aspirin component of our proposed trial differs from the doctors' trials in two major respects. First, our trial will be based on men at substantially increased risk of IHD. Secondly, we shall be using a considerably lower dose of aspirin than either of the doctors' trials, especially the British. This lower dose will certainly reduce the incidence of gastro-intestinal side-effects and might also reduce the risk of cerebral haemorrhage. On theoretical grounds, the lower dose may also be more effective in preventing IHD.

In the ISIS-2 trial of aspirin and streptokinase in a factorial design, anticoagulation was also planned in the majority of patients recruited and actually used in the large majority of those for whom it was planned. This has enabled an assessment of any additional risk of bleeding attributable to aspirin in patients on anticoagulants. The findings were:

ISIS-2: Proportion (%) of patients in whom anticoagulation
was planned experiencing bleeding episodes

	Aspirin N:5851	Placebo N:5842
Major	0.4	0.4
Major and minor	3.3	2.5

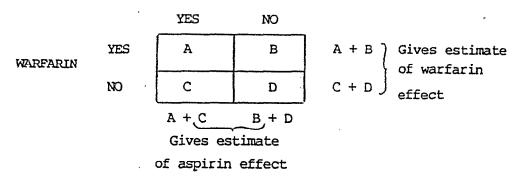Source: personal communication from 400 participating hospitals

Thus, there was no excess of major bleeding episodes attributable to aspirin
(major episodes being defined as those requiring transfusion). Of the 10
episodes of cerebral haemorrhage observed, 5 occurred in those on aspirin
and 5 in those on placebo treatment. There may have been an increase in the
incidence of minor bleeding episodes. Bearing in mind that both the
intensity of anticoagulation and the dose of aspirin were higher in ISIS-2
than we are proposing, these findings on the concurrent use of anticoagu-
lants and aspirin are reassuring. It should also be noted that the main
result of ISIS-2, i.e. benefits of about 20% and 25% for aspirin and
streptokinase respectively and a benefit of 40% in those treated with both
(personal communication from 400 participating hospitals), provides very
strong justification for our own approach of modifying both platelet
activity and fibrin formation.

FACTORIAL DESIGN

The evaluation of low dose aspirin, in addition to low dose warfarin, could
be approached in two ways. One would be to start what would in effect be a
completly separate trial. High risk men could be identified as they have
been so far and then randomized either to the warfarin or the aspirin trial.
From then on, however, there would be two unrelated trials. A major disad-
vantage of this approach is that the numbers required would be twice a great
as for a single trial and that costs would, therefore, also be nearly twice
a much.

The alternative is to evaluate both low dose warfarin and low dose aspirin
in the same trial, using a factorial design thus:

ASPIRIN

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                    YES        NO
              ┌──────────┬──────────┐
        YES   │    A     │    B     │    A + B ⎤  Gives estimate
WARFARIN      │          │          │          ⎥  of warfarin
        NO    │    C     │    D     │    C + D ⎦  effect
              └──────────┴──────────┘
              A + C        B + D
              Gives estimate
              of aspirin effect
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There would be four treatment groups - one (B) on warfarin alone, one (C) on aspirin alone, one on both warfarin and aspirin (A) and one on placebo treatment (D). A factorial design is efficient in that it enables results on two drugs to be obtained from a trial that is no bigger than a trial to evaluate only one of the agents, provided there is no substantial negative interaction. A second advantage is that the value of the two drugs used simultaneously can be assessed. It would clearly be useful to know whether, by modifying both fibrin production and platelet activity, warfarin and aspirin together resulted in a larger effect than either of them separately. This could not be demonstrated in two separate trials. A third advantage (which particularly appeals to the general practitioners in the General Practice Research Framework (GPRF) through which the trial would be conducted) is that 75% of the participating patients would receive active treatment of one kind or another, instead of 50% in a single agent trial.

A potential disadvantage of the factorial design is that one group takes both drugs and is therefore exposed to the potential hazards of both. It should be emphasised that the proposed aspirin dose, at 75 mg daily, means that participants would be taking the equivalent of only a little more than one conventional aspirin tablet (325 mg) weekly. To obtain further information about the possible effects of low dose aspirin on its own and also to study the effects of low dose warfarin and low dose aspirin used simultaneously, Dr Christopher Hawkey in Nottingham undertook a study at our request to measure the bleeding associated with (1) warfarin-induced anticoagulation of the intensity used in our trial (2) 75 mg aspirin (Junior Aspirin formulation) (3) both together and (4) no treatment i.e. the basal rate. Bleeding into gastric washings obtained by intubation was quantified using the orthotolidine reaction. The study was carried out, with ethical committee approval, in 20 medical students. The results were as follows:

	Bleeding, μL/10min
Basal	0.60
Warfarin, INR 1.6	0.59
Aspirin, 75 mg o.d.	1.26
Warfarin + aspirin	1.02

In summary, there was no significant increase in gastric bleeding associated with anticoagulation of the intensity used in the trial which is, of course, additional and welcome evidence of the probable safety of low dose warfarin. Aspirin on its own produced a small though significant increase ($p < 0.03$) in bleeding. Aspirin and warfarin together led to no more bleeding than aspirin on its own, so there appeared to be no interaction between the two .gents so far as gastric bleeding is concerned. The reassuring ISIS-2 results have already been referred to.

THE PROPOSED TRIAL

For simplicity, and with exceptions which are considered separately later on, the formal specification of the trial will sometimes be considered for one agent only, exemplified by warfarin, since the statistical requirements for a factorial trial are, under ideal circumstances, the same as those for a trial of a single agent.

The objective of the trial would be to demonstrate a reduction of 30% in the incidence of IHD, whether non-fatal (myocardial infarction) or fatal (coronary death), attributable to warfarin or aspirin, significant at the 1% level and with 90% power.

This trial would require the recruitment of at least 4,500 high risk men aged between 45 and 64 into the treatment phase but, for reasons considered later on, we propose the recruitment of 6,000 men aged between 45 and 69. The definition of high risk is given in the report of the feasibility study (European Heart Journal, ~~in press~~ attached). Meade et al, 1988, 9, 836-843.

STATISTICAL CONSIDERATIONS

Benefit to be detected. The justification for setting the warfarin benefit to be detected at 30% depends, first, on the benefit predicted from NPHS data of a reduction in VII_c from about 117% to 70%. Using the independent association between VII_c and risk of IHD within the next five years, a

reduction of 50% would be expected. This may well be an exaggeration bearing in mind that the figure is based on an estimate derived from the same study in which the association has been demonstrated. On the other hand, the true association between VII_c and IHD has almost certainly been underestimated as a result of the high level of within-person variability in VII_c. Taking these and other considerations into account, we initially proposed a benefit of 35%, corresponding to about 30% in practice to take account of loss of power due to the observed rate of withdrawals from randomized treatment in the pilot study. The design and specification of the trial also imply a benefit of 30% to be detected for aspirin.

Placebo event rate. A crucial figure in estimating sample size is the expected event rate in the placebo group. We are fortunate in having the actual five year placebo event rate (10.8%) for IHD in participants aged 45 to 64 in the MRC's hypertension trial, i.e. in the same population in which the proposed warfarin/aspirin trial would be carried out (45). We estimate that the placebo event rate over a five year period in the latter would be 11.4%.

Modifications. There are two substantial modifications to the procedures used in the pilot trial that we would introduce which would increase the power of the trial:

(i)   We would extend the age range to 69. Raising the upper age limit for entry to 69 would increase the trial's power to 96% (or reduce the numbers required to about 3,600 if the power specification were maintained at 90%). (Participation beyond the age of 74 (see (ii) below) would be specially reviewed case by case and a decision made after discussions between the doctor and the patient.)

(ii)   A second way of increasing the trial's power would be to follow all participants up until the end of the trial, regardless of the time of entry. The minimum follow-up would be for five years but since a four year recruitment period is envisaged, those entered first could be followed-up for up to nine years. The total number of man-years of observation would be about 40,000 compared with 30,000 if there were a uniform five year follow-up period. In a trial of 4,500 patients, this would increase the power to detect a 30% reduction to 97% and would provide about 87% power to detect a reduction of 25%. (If - see

later - the trial recruited 6,000 patients, we could detect a 23% reduction in events with 90% power.)

Negative interaction. An important consideration pointing to as large a trial as possible is the need to allow for a negative interaction between warfarin and aspirin which would reduce the power of the test for the main treatment effects. The basic specification calls for a trial on 4,500 patients. In order to take the factorial design into account and to allow for the possibility of a moderate negative interaction, we propose to recruit 6,000 patients. Apart from points already considered, any estimate of benefit will be subject to confidence limits and the larger the trial the smaller these will be.

CONDUCT OF THE TRIAL

Apart from the introduction of aspirin, the implications of which are considered later on, and the changes described in (i) - (ii) of the previous section, the general conduct of the trial would, with only minor alterations, follow the procedures set out in the report of the pilot trial. These procedures are the result of experience over the last four years and, with appropriate modifications during this period, work well.

Population. The trial would be based on men aged between 45 and 69 on the lists of doctors in practices in the MRC's General Practice Research Framework (GPRF).

Communication with hospitals. As indicated in the report of the pilot trial, approval is sought from the ethical committee in each District concerned. Because procedures still differ from one District to another, this is very time-consuming but does carry the advantage of alerting clinicians to the trial and its possible consequences for them. One is the need to try to avoid patients being admitted for elective surgery before trial treatment has been discontinued. In the early stages, this did occur twice and the patients had to return home for re-admission later on (fortunately, in each case, very soon afterwards). Over recent months, with a considerably larger number of men in the study, this difficulty has been avoided largely due to the special measures taken by the Framework doctors over patients on waiting lists or being referred to hospital, coupled with awareness and acceptance of the trial by hospital staff. Similar steps have been taken by several of the Framework practices over communication with

local dentists. Another point of communication is to ensure that those responsible for emergency admissions, particularly cardiologists, are aware of the trial if they are contemplating thrombolytic therapy. In discussion about this point, it is generally agreed that since the purpose of the trial is to prevent high risk patients needing treatment of this kind, the growing use of thrombolytic therapy is not a valid argument against it but it is a development that needs to be borne in mind and allowed for.

Recruitment, follow-up and laboratory tests. We would plan recruitment over a four year period from mid-1988. The establishment of age-sex registers, the note-search stage, screening and the initiation and stabilization of treatment would, with one exception, be as described in the progress report. The exception is that we would confine VII_c measurements to screening, entry and annual follow-up visits and to a random sample of the specimens sent for INRs. The main reason for this modification is to reduce both staff and recurrent expenditure costs. By now, the pilot trial has provided very comprehensive information about the rate of change in VII_c due to treatment. In addition, dose changes have depended mainly on the response of the INR, since the effects of warfarin on other vitamin K dependent clotting factors besides VII_c also have to be allowed for. We have compared the relationship between VII_c and INR in our extensive pilot trial data on this point, from which it is clear that the use of the INR for dose change purposes is justified. Thus, while the relationship between VII_c and IHD is a major part of the scientific case for the trial, the trial itself can be managed in practice by relying only on the INR.

Risk scoring and selection for treatment phase. The risk scoring system, briefly described in the report of the pilot trial, is based on family history of IHD, current smoking habit, systolic blood pressure, body mass index and cholesterol, VII_c and fibrinogen levels. Apart from family history, these variables are weighted according to the strength of their independent associations with IHD in NPHS and a risk score for each man is thus derived. Family history was not recorded in NPHS, the only information of this kind being age of parents or age at parental death. After reviewing studies in which family history has been included, we have derived an arbitrary but probably conservative weighting for family history.

Terminating events. The procedure for detecting and assessing terminating events i.e. myocardial infarction, coronary death, stroke, other

cardiovascular events and cancer, would be the same as that used in the mild hypertension trial (45).

Drug interactions with warfarin. We have made arrangements to identify and deal with the possible consequences of the interaction of other drugs with warfarin and have done this with advice from clinical pharmacologists. The main guidance, both for general practitioners and patients, is the list of drugs interacting with warfarin reproduced in full on the "carrying card" based on a review in the Adverse Drug Reaction Bulletin but up-dated from time to time in the light of new reports, etc. This is supplemented by circulars to participating practices drawing attention to any recent developments. We have gone into particular detail over the use of non-steroidal anti-inflammatory agents (NSAIDs).

Inclusion of aspirin. Some changes would be necessary to allow for the use of aspirin, 75 mg daily, as one of the active agents. We would continue rigorously to exclude patients on the grounds of any symptoms that might suggest peptic ulceration. Sensitivity to salicylates would be added to the reasons for ineligibility and would be sought at screening and at the entry medical examination as well as during the note-search stage. The explanatory leaflet given to high risk men at the time of their invitation to enter the treatment phase would be modified to include information about low dose aspirin and the factorial design. The carrying card would also be modified in these respects. Advice in the card about alternative analgesics would be re-worded to continue to emphasise the particular importance of avoiding salicylate-containing preparations while, at the same time, drawing attention to the use of the trial's low dose (and thus explicitly avoiding any perceived contradiction that might otherwise seem to exist). To avoid possible confusion between warfarin and aspirin tablets (or their matching placebos), warfarin tablets would continue to be provided, as they have been during the pilot study, in capped plastic tubes while the aspirin tablets would be provided in blister packs. Subject to experience in a small pilot stage for the factorial trial, due to begin shortly, patients would start on both warfarin and aspirin tablets (or placebo) at the same time, i.e. at the first treatment phase visit.

Applicability of results. At this stage, it is difficult if not impossible to say precisely what the practical applicability of the results would be. Obviously, this would be largely determined by the size of any benefit

conferred by the two agents, separately or combined, and the balance between these benefits and any hazards. The value of other agents in trials reporting over the next few years would also be relevant. It is, however, clear from discussion with Framework doctors that they would consider the use of low dose warfarin and/or low dose aspirin for selected high risk individuals in their clinical management if the trial showed benefits.

ANALYSIS AND MONITORING

The main analyses would be by intention to treat, i.e. as randomized, though on-treatment analyses would also be performed. P values would be adjusted for multiple inspections of the data. Sub-group analyses for different effects by age, smoking habit and according to change in VII_c and entry risk score would also be performed. Because risk (within the top 20% of the risk score distribution) may, from NPHS data, rise quite markedly, the last of these specified sub-group analyses could be of considerable importance. For if the extent of increased risk in, say, the top 10% outweighed the conse-quences of the smaller numbers in the analyses, a beneficial treatment effect in the top 10% might be detected before it was clearly demonstrated in the trial group as a whole, and might lead to an earlier decision about terminating the trial.

We anticipate that the incidence of serious bleeding would be low and that it would require a separate monitoring system. We propose that each pos-sible case of serious bleeding should be referred to the Chairman of the monitoring committee who would, of course, know the treatment group and who would if necessary consult other members of the monitoring committee.

The main specification of the trial deals with the effects of treatment on IHD. As the mild hypertension trial showed, however, decisions about ending or continuing a trial may well depend on considerations besides the main objective. Possible developments of this kind in the warfarin/aspirin trial that might need to be taken into account are:

(i)   Treatment might result in an increase in serious bleeding episodes at the same time as a decrease in IHD and other thrombotic events. The balance between these two effects would obviously need careful assess-ment from an early stage.

(ii)   Besides a benefical effect on IHD, treatment might also reduce the incidence of cerebrovascular disease.

(iii)   It is possible that warfarin treatment might be associated with a small decline in the incidence of cancer. This and (ii) might affect analyses based on mortality from all causes.

(iv)   One agent might reduce the incidence of IHD by a greater amount than the other. One trial treatment might therefore have to be discontinued and a decision made about the continuation of the trial to complete the assessment of the other agent, and on the most appropriate way of doing this.

(v)   There might be a positive interaction, warfarin and aspirin together significantly reducing IHD incidence before a significant effect of either agent on its own had been demonstrated.

Sir Stanley Peart has agreed to be Chairman of the monitoring committee. This committee would receive the interim analyses of the main and subsidiary results, consider the ethical case for continuing or terminating the trial in the light of these results and advise the Director of the MRC Epidemiology and Medical Care Unit accordingly.

The day to day conduct of the trial would be the responsibility of EMCU and it would be important that those concerned were unaware of the indications of the main results. During the pilot trial, collection of information about terminating events has been the responsibility of a doctor not otherwise involved in the anticoagulant trial in conjunction with the trial's statistician. The statistician would, of course, know what the main results were and would be responsible for communicating them to the monitoring committee at the appropriate times. There have by now been some terminating events and it is clear that although the statistician and the rest of the EMCU group are in daily contact with one another, confidentiality of the results to one or two individuals within EMCU can be ensured.

ETHICAL CONSIDERATIONS
The low dose warfarin trial has been approved by all the district ethical committees to which it has been submitted. In addition, the Committee on Ethical Issues in Medicine set up by the Royal College of Physicians and

convened by Sir Douglas Black was asked for advice about the way in which the balance of potential benefits and risks is explained to men entering the treatment phase. The Committee endorsed the approach we have adopted, which is to make all the information on possible benefits and possible hazards available to the general practitioners and to allow them considerable discretion, from patient to patient, about the detail in which they use this information (provided - as well as the explanatory leaflet given to all the men entering the treatment phase - they mention the possibility of an increased risk of bleeding). Finally, EMCU approached the MRC for an interim opinion about the progress of the trial in the light of practical experience. This request was considered by the Office and the cardiologist on the Board at the time whose view was that, on the basis of the growing scientific case for the trial, it might well be wrong not to proceed with it.

The inclusion of aspirin would be included in all future submissions and, as a supplementary revision or addition, in further submissions to committees that have already considered the warfarin trial.

<center>COSTS</center>

We have assumed that 6,000 men will enter the treatment phase and that these will have been recruited from rather more than 60,000 attending for screening. We have assumed a four year recruitment period and a six year follow-up period (though, strictly, this will be five years) in order to allow for some slippage of the proposed schedule. We have also assumed that patients entering the trial early on will be followed up until the trial ends, i.e. for more than five years (see earlier). A total sample size of only 4,500 and/or a decision not to follow-up those patients recruited earliest for more than five years would reduce costs. We believe the costs are realistic since they are based on actual experience during the pilot trial. Even so, there is, inevitably, a margin of uncertainty around each of the sub-headings and we have tended to over- rather than under- estimate costs. The figures do not allow for inflation or for pay awards. The costs can be summarised under three main headings:

1.   Costs entirely attributable to the warfarin/aspirin trial. The largest single cost is for payment to the clinic nurses. They carry out the note search, the screening clinics and the treatment phase clinics and deal with

day to day queries. Payments to the doctors are for entry medical and annual follow-up examinations. For both the nurses and the doctors, payment is at agreed hourly rates. Most of the post/phone item is for the transport of blood samples and trial forms to EMCU. Miscellaneous expenditure includes time spent by practice managers and practice office supplies. Stock includes laboratory supplies, stationery and trial forms.

2.   The proportion of costs for general GPRF services that are attributable to the warfarin/aspirin trial. ECG coders refers to payments for coding ECGs (as in the mild and eldery hypertention trials). Overheads include heating costs for clinic rooms. CRC parcels refers to payments to CRC for dispatching supplies to clinics. R-Z repairs refers to maintenance of random-zero sphygmomanometers (again, as in the mild and elderly hypertension trials). Centrifuges refers to the supply and maintenance of centrifuges to the GPRF practices for the separation of plasma. These costs could be met from our British Heart Foundation grant.

3.   Laboratory costs. This section shows EMCU laboratory costs over and above the current level of provision through our recurrent expenditure allocation.

Staff. We would need two additional technical staff members for work in the laboratory and would propose to fund these from the balance of our British Heart Foundation grant, which has now been renewed until the end of 1991. We would also need additional clerical and data-processing staff, the numbers rising and then falling in line with changes in the work load. Until 1990 or 1991, these requirements can probably be met by releasing posts we have frozen during the last two or three years and by redeployment of other posts. It might be possible to cover the rest of the trial, particularly during its maximum work-load, in the same way but this would have to be reviewed in due course.

1. Costs entirely attributable to the warfarin/aspirin trial

	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	TOTAL
GPRF Nurses	28786	103490	160789	207988	230691	206375	197844	198005	198167	160880	1693015
GPRF Doctors	991	9320	20647	31951	42299	45676	45827	45827	45827	37002	325364
Post/Phone	3523	9880	12439	13938	12622	7981	7114	7114	7114	5744	87468
Stock	13031	21809	25587	28938	21930	15700	15504	15504	15504	9552	183060
Miscellaneous	5061	14626	21386	26301	26500	22246	20431	20431	20431	18715	196128
Total per year	51392	159125	240848	309117	334042	297979	286719	286880	287042	231981	2485036

2. Costs for general GPRF services attributable to the warfarin/aspirin trial

	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	TOTAL
ECG Coders	1586	4552	7472	10274	11735	11676	11676	11676	11676	7367	89690
Overheads	1800	3600	5400	7200	7200	7200	7200	7200	7200	7200	61200
CRC Parcels	1080	2160	2808	3672	3024	3024	2592	2592	2592	2592	26136
R-Z Repairs	441	882	1323	1764	1764	1764	1764	1764	1764	1764	14994
Centrifuges	3816	540	756	972	972	972	972	972	972	972	11916
Total per year	8723	11734	17759	23882	24695	24636	24204	24204	24204	19895	203936

3. Laboratory costs

	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	TOTAL
Total per year	12308	20159	23597	26864	18391	14010	13855	13855	13855	8553	165448

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